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ORIGINAL REPORT

Surveillance After Initial Surgery for Pediatric and Adolescent Girls With Stage I Ovarian Germ Cell Tumors: Report From the Children's Oncology Group

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To determine whether overall survival (OS) can be preserved for patients with stage I pediatric malignant ovarian germ cell tumor (MOGCT) with an initial strategy of surveillance after surgical resection.

Patients and Methods
Between November 2003 and July 2011, girls age 0 to 16 years with stage I MOGCT were enrolled onto Children's Oncology Group study AGCT0132. Required histology included yolk sac, embryonal carcinoma, or choriocarcinoma. Surveillance included measurement of serum tumor markers and radiologic imaging at defined intervals. In those with residual or recurrent disease, chemotherapy with compressed PEB (cisplatin, etoposide, and bleomycin) was initiated every 3 weeks for three cycles (cisplatin 33 mg/m^2 on days 1 to 3, etoposide 167 mg/m^2 on days 1 to 3, bleomycin 15 U/m^2 on day 1). Survivor functions for event-free survival (EFS) and OS were estimated using the Kaplan-Meier method.

Results
Twenty-five girls (median age, 12 years) with stage I MOGCT were enrolled onto AGCT0132. Twenty-three patients had elevated alpha-fetoprotein (AFP) at diagnosis. Predominant histology was yolk sac. After a median follow-up of 42 months, 12 patients had evidence of persistent or recurrent disease (4-year EFS, 52%; 95% CI, 31% to 69%). Median time to recurrence was 2 months. All patients had elevated AFP at recurrence; six had localized disease, two had metastatic disease, and four had tumor marker elevation only. Eleven of 12 patients experiencing relapse received successful salvage chemotherapy (4-year OS, 96%; 95% CI, 74% to 99%).

Conclusion
Fifty percent of patients with stage I pediatric MOGCT can be spared chemotherapy; treatment for those who experience recurrence preserves OS. Further study is needed to identify the factors that predict recurrence and whether this strategy can be extended successfully to older adolescents and young adults.

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INTRODUCTION

In the prechemotherapy era, even localized malignant nongerminomatous ovarian germ cell tumors were associated with survival of only 20%.[1] The advent of platinum-based chemotherapy for testicular cancer in 1977 dramatically improved survival[2] and was subsequently applied to all extracranial sites in children.[3] Although survival for those with early-stage pediatric malignant germ cell tumors treated with platinum-based chemotherapy is currently > 90%,[3,4] life-threatening late effects of chemotherapy remain a challenge. Renal impairment, neurotoxicity, and hearing loss are well-recognized toxicities in pediatric patients treated for germ cell tumors.[5] Recent long-term follow-up studies of men with testicular cancer have demonstrated that the risk of cardiovascular disease and second malignancy is increased two-fold[6]; similar long-term studies of late effects do not yet exist for children, although the treatment regimens for adult and pediatric germ cell tumors are nearly identical. Among men who were treated for testicular cancer with cisplatin-based chemotherapy at age 20 years, the rate of second malignant neoplasm (SMN) was 50% by age 75 years, analogous or even higher than the rate of SMN seen in patients with Hodgkin lymphoma.[6] Because as many as 75% of men with stage I testicular cancer

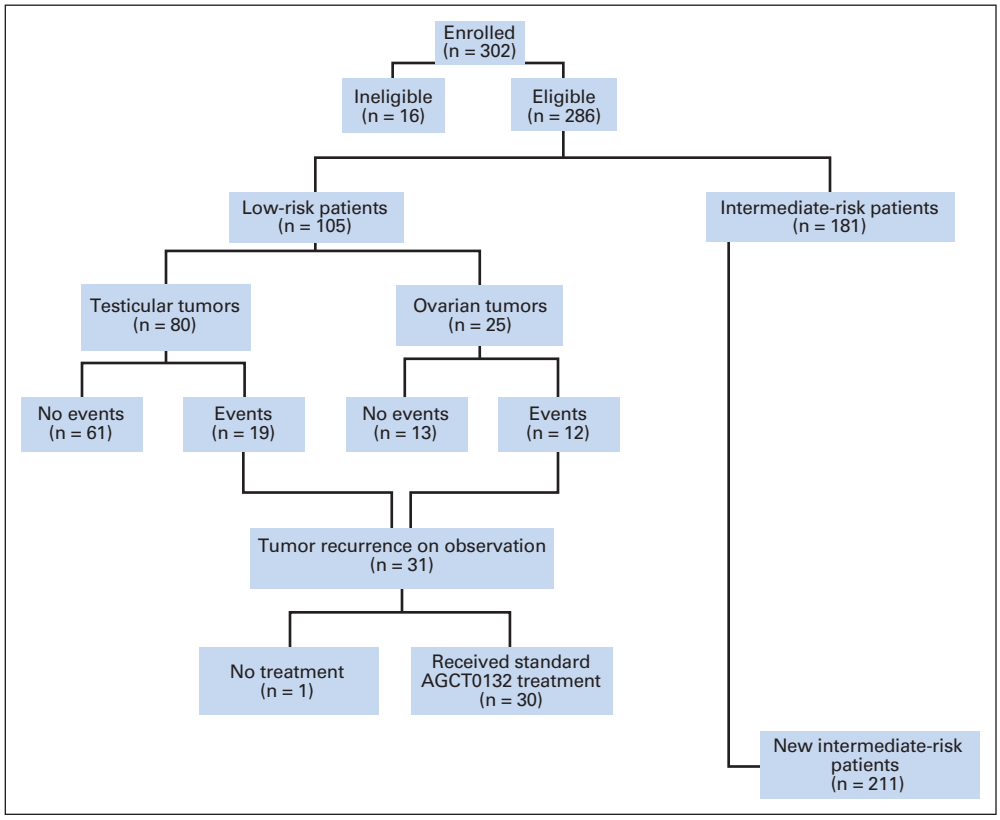

Fig 1. Patient flow diagram: low- and intermediate-risk patients.

are cured with surgery alone, and salvage with chemotherapy is successful in those who experience recurrence, surveillance is now an accepted standard of care in men with stage I testicular cancer.[7] These findings, and the recent success of a surgery-only watch-and-wait strategy for stage I testis tumors in prepubertal boys,[8] motivated the design of our study to assess whether a surveillance strategy with strictly defined surgical guidelines could be extended to stage I malignant ovarian germ cell tumors (MOGCTs) in pediatric and adolescent girls.

PATIENTS AND METHODS

Patients

On the basis of the results of the last intergroup pediatric germ cell trial, INT-0016,[3] the Children's Oncology Group (COG) protocol AGCT0132 divided pediatric germ cell tumors into three categories: low, intermediate, and high risk (Fig 1). Low-risk patients had stage I ovarian and testicular germ cell tumors; AGCT0132 prescribed a surveillance strategy for low-risk gonadal tumors. Intermediate-risk patients were defined as having stage I to II extragonadal, stage III ovarian, or stage III to IV testicular tumors; these patients received three cycles of compressed pediatric BEP (bleomycin, etoposide, and platinum; PEB [cisplatin, etoposide, and bleomycin]). PEB differs from adult BEP; bleomycin is administered once per cycle with PEB versus once per week with BEP. High-risk patients, defined as having stage III to IV extragonadal tumors, were excluded from this trial. Patients were required to have one of the following histologic elements: yolk sac, choriocarcinoma, or embryonal carcinoma; pure seminoma/dysgerminoma and immature teratoma and/or malignant somatic transformation were excluded. Institutional review board approval was obtained at participating centers.

Required data for enrollment onto the low-risk stratum of AGCT0132 included adherence to surgical guidelines (Table 1), submission of operative note and surgical checklist, metastatic imaging at diagnosis, and central pathology review. Patients were to be enrolled within 6 weeks of initial diagnosis. Patients could be enrolled onto the low-risk stratum if their tumor markers were elevated but not rising. If tumor markers failed to decline according to a 7-day half-life up 6 weeks after diagnosis, or if central review of submitted materials indicated the patient did not have stage I disease, the institutional investigator was to start administering therapy, and the patient was not considered in the analysis of the low-risk strategy.

Treatment

The surveillance strategy for patients with stage I disease managed with surgery only required measurement of serum markers alpha-fetoprotein (AFP) and beta human chorionic gonadotrophin (β-HCG) every 3 weeks through week 9, every month from months 2 to 6, and every 3 months from months 6 to 24. Patients in the surveillance stratum whose serum tumor markers failed to decrease at the expected rate after initial surgery or had radiologic evidence of relapse were transferred to the intermediate-risk stratum. Chemotherapy for intermediate-risk patients consisted of three cycles of

Table 1. COG Surgical Guidelines for Ovarian MGCT

Guideline
Collection of peritoneal fluid or washings for cytology
Examination of peritoneal surfaces with biopsy of any abnormal areas
Palpate retroperitoneal lymph nodes; biopsy only if abnormal (firm or enlarged)
Inspect omentum; biopsy only if abnormal
Palpate/inspect opposite ovary; biopsy only if abnormal
Complete resection of involved ovary intact (no capsule entry on field) with sparing of fallopian tube if not involved

Abbreviations: COG, Children's Oncology Group; MGCT, malignant germ cell tumor.

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compressed PEB. The compressed regimen included: cisplatin 33.3 mg/m^2 on days 1 to 3, etoposide 167 mg/m^2 on days 1 to 3, and bleomycin 15 U/m^2 on day 1.

Data monitoring during the study revealed a higher-than-expected event rate in the low-risk stratum, and enrollment was temporarily suspended. The initial statistical design had employed a model predicting that failures would occur at a uniform rate for the first 3 years after enrollment. Data from the previous study, INT-106, became available after AGCT0132 was opened and demonstrated that 80% of failures occurred within the first year after enrollment. The low-risk arm was reopened with a revised statistical modeling of predicted time to failure. Rapid review of eligibility data was conducted by a COG study surgeon within 72 hours of enrollment, including review of the operative note, pathology report, surgical checklist, and imaging findings. Reassignment to a higher stage based on this rapid review was at the discretion of the enrolling institution.

Statistical Analysis

Event-free survival (EFS) was measured from time of enrollment to disease progression, diagnosis of an SMN, death, or last patient contact, whichever occurred first. Patients who did not experience an EFS event were censored at last contact. Overall survival (OS) was measured from time of enrollment to death or last patient contact, whichever occurred first. Patients who did not experience an OS event were censored at last contact. Survivor functions for EFS and OS were estimated using the Kaplan-Meier method.[9] CIs for the survivor functions were calculated using complementary log-log transformation.[9]

The AGCT0132 low-risk stratum was designed to enroll 126 patients with stage I testicular or ovarian cancer over 6 years, with 1 year of follow-up after the last enrollment. The estimated survival curve was to be compared with a piecewise exponential failure model with 5-year survival of 95% using the Woolson one-sample log-rank test.[10] A one-sided test of .10 indicated a significant departure from survival model. The design had 80% power to detect a decrease in 5-year survival to 83%. Interim monitoring of risk of death was performed using the method of Lan and DeMets[11] annually, with a spending function that was linear in information time. In addition, interim monitoring of the risk of EFS was conducted. At the time of primary survival analysis, the estimated EFS curve was to be compared with a piecewise exponential failure model with 5-year EFS of 70% using the Woolson one-sample log-rank test.[10] A one-sided test of .10 indicated a significant departure from the EFS model. An EFS of 70% was chosen because this was greater than that observed for men with low-risk testicular cancer, and there was uncertainty regarding whether pediatric patients experiencing disease progression could as readily successfully respond to salvage chemotherapy as adult patients. Interim monitoring of risk of EFS event was performed annually using the method of Lan and DeMets,[11] with a spending function that was linear in information time. If the interim monitoring rule indicated either excessive risk of death or EFS event, the trial was referred to the COG Data Safety Monitoring Committee for possible termination of enrollment.

Prognostic variables considered in the analysis included serum AFP obtained before tumor surgery ($< 10{,}000$ *v* $\geq 10{,}000$ IU/L), age at diagnosis (≤ 10 *v* ≥ 11 years), maximum tumor dimension (≤ 20 *v* ≥ 21 cm), and histology (pure yolk sac tumor [YST] *v* all others). Possible association between risk for EFS event and prognostic factor was assessed using the log-rank test. Characteristics associated with *P* values $\leq .05$ were considered significantly associated with risk of EFS event.

RESULTS

AGCT0132 was opened in November 2003 (Fig 1). Enrollment of patients onto the low-risk stratum was stopped in January 2010 because there was significant evidence that 3-year EFS was $< 70\%$. A total of 105 eligible patients were enrolled onto the low-risk stratum of AGCT0132, including 80 male patients with stage I testis tumors and 25 female patients with stage I ovarian tumors. Results of the male patients in the low-risk stratum and of the patients in the intermediate-risk stratum will be reported elsewhere. The 25 female patients with stage I ovarian tumors undergoing follow-up with surgery and surveillance form the basis for this report.

The surgical reviewer's assessment of stage was concordant with the institutional assessment of stage in 21 patients and was discordant

Table 2. Patient Demographic and Clinical Characteristics

Characteristic	No.	%
Age at enrollment, years		
≤ 10	8	32.0
≥ 11	17	68.0
Median	12	
Range	0-16	
Race		
White	16	64.0
Black	5	20.0
Asian	2	8.0
Unknown	2	8.0
Tumor marker (AFP)		
AFP elevated at diagnosis	23	
Median AFP level at diagnosis	3,715	
Range	19-2,220,000	
AFP ever normalized		
No	9	39.1
Yes	14	60.9
Time to normalization, days		
Median	22.5	
Range	12-153	
Histology		
Pure YST	8	32.0
YST plus MT only	3	12.0
YST plus IT*	7	28.0
Mixed malignant†	7	28.0
YST at diagnosis, %		
< 1	2	8.0
1-4	6	24.0
5-49	4	16.0
50-99	4	16.0
100	8	32.0
Unknown	1	4.0
Median	37.5	
Range	0.5-100	
Tumor size, cm		
1-10	1	4.0
11-20	14	56.0
21-30	6	24.0
31-35	1	4.0
Unknown	3	12.0
Median	18.8	
Range	10-33	
Stage review		
Concordant	21	84.0
Discordant	4	16.0
Relapse		
No. of patients	12	48.0
Median time to relapse, days	64.5	
Range	31-237	

Abbreviations: AFP, alpha-fetoprotein; IT, immature teratoma; MT, mature teratoma; YST, yolk sac tumor.
*IT had to be grade 2 or 3; patients who had YST, IT, and MT were also included in this group.
†Includes one patient who was not classified.

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in four patients; the enrolling institution in all four cases elected to have patients continue in the low-risk stratum despite the results of the eligibility review. The reasons for the discordance between the enrolling institution and study physician review resulted from the findings of tumor rupture documented in the operative notes and/or pathology reports in three patients and the failure to collect peritoneal cytology in the remaining patient.

Two thirds of patients were age > 10 years at diagnosis; the oldest patient enrolled onto the trial was age 16 years (Table 2). AFP was elevated in all but two patients at diagnosis. At central pathologic review, presence of a malignant component was confirmed in 24 of 25 patients. In one case, the central reviewer did not agree that there was a microscopic focus of YST within the immature teratoma, but the patient was not removed from the protocol by the treating institution, as was its purview. YST was the primary malignant histology; eight patients had pure YST, three had YST mixed with mature teratoma, and seven had YST mixed with immature teratoma. Tumor size was available in 22 patients and ranged from 10 to 33 cm (median, 18.8 cm).

EFS at 4 years after enrollment was 52% (95% CI, 31% to 69%), and OS was 96% (95% CI, 74% to 99%; Fig 2). Tumor events requiring initiation of salvage chemotherapy occurred in 12 low-risk patients from 1 to 8 months after initial surgery (median, 2 months; Table 3). All patients experiencing recurrence had an increase in their AFP level. In four patients, despite the rise in AFP, no mass could be detected by imaging. Among the remaining eight patients, five had disease localized to the pelvis, two had metastatic disease (liver and pleura), and one had a site of relapse not specified by the institution. All patients responded to three cycles of PEB chemotherapy. Two patients had a second relapse after initial PEB therapy. The first patient had a second relapse within 6 weeks of completing the initial three cycles of PEB and was treated with alternate chemotherapy with intermittent normalization of markers but new appearance of progressive disease by imaging in multiple places within the abdominal cavity. Biopsy was performed after completion of her second regimen of chemotherapy and showed viable YST. She died as a result of tumor progression at 16 months after initial diagnosis. The second patient was treated with taxol, ifosfamide, and carboplatin after enrollment onto COG study AGCT0521 and remained alive and disease free 2 years after completing salvage therapy.

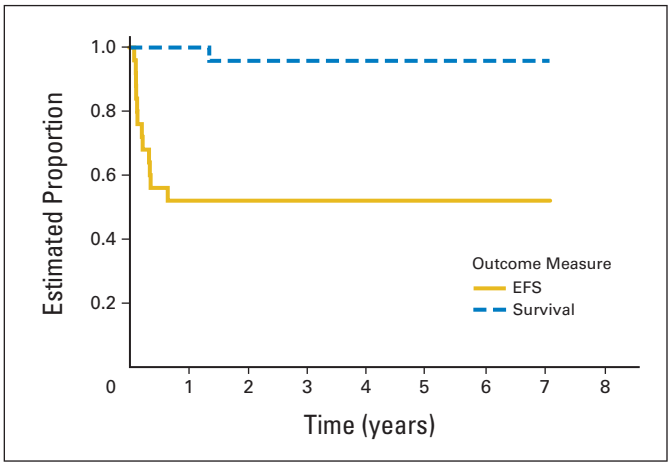

Fig 2. Event-free survival (EFS) and overall survival of pediatric and adolescent female patients with stage I ovarian germ cell tumors.

Risk of relapse was not significantly related to age, preoperative AFP, histology, or tumor size (data not shown). In 18 girls with concordant pathology and intact tumor capsule, additional detailed pathology comment was available. Events were seen in six of 15 girls whose primary tumor had an uninvolved capsule compared with two of three girls with evidence of capsule penetration (partial invasion of intact capsule wall).

DISCUSSION

In this study of 25 girls with stage I tumors treated initially with close surveillance, 12 girls experienced either failure of tumor marker decline or evidence of relapse and required initiation of chemotherapy; 11 of 12 received successful salvage chemotherapy (4-year EFS, 52%; 95% CI, 31% to 69%; 4-year OS, 96%; 95% CI, 74% to 99%). All events occurred within the first 8 months after surgery, with a median of 60 days, and all recurrences were accompanied by rising AFP. The prognostic significance of AFP, tumor size, age, and histology was null; however, the evaluation of prognostic factors was limited by the small number of individuals and EFS events observed in this cohort.

The so-called hidden site in the abdominal cavity allows ovarian germ cell tumors to reach a greater size before detection than their testicular counterpart. The risk of tumor rupture before or at time of surgery is significant, with the potential for contamination of a large cavity. Because the risk of malignancy for ovarian neoplasms in childhood and adolescence is only 10% to 20%,[12] a surgeon may fail to consider the possibility of malignancy at the time of surgery, resulting in incomplete staging, particularly failure to obtain peritoneal cytology. A study from the Centre Leon Berard and Institut Curie in France[13] examined the impact of incomplete staging on risk of relapse in 38 patients (age 0.4 to 27.9 years) with stage I MOGCT. Retrospective analysis revealed incomplete staging in 56%. These patients were classified as having stage Ix disease. This study included girls with evidence of tumor rupture or positive peritoneal fluid cytology (Ic according to International Federation of Gynecology and Obstetrics staging [FIGO staging]). These patients would not have been classified as having stage I disease by COG criteria; they would have be classified as having stage II and III disease, respectively, and treated with chemotherapy at the time of diagnosis. In the French study, relapses occurred only in patients with stage Ic or Ix disease (stage Ia, zero of eight; Ic, three of three; Ix, five of 13 patients). The clustering of events in these groups is notable and reinforces the need to assess compliance with surgical guidelines before assignment of tumor stage and treatment plan.

Despite these challenges, a surgery-only approach for pediatric nongerminomatous MOGCT in girls age < 18 years has been applied in several centers. The SFOP (Société Française d'Oncologie Pédiatrique) study from France[14] included 12 girls with stage I ovarian tumors similarly managed. There were six relapses. Five were received successful salvage chemotherapy; there was one death resulting from nonresponse. The CCSG (Children's Cancer Study Group) study from the United Kingdom[15] included nine girls with stage I ovarian tumors treated with surgery only. Three experienced relapse, and all underwent successful salvage chemotherapy. The MAKEI (Maligne Keimzelltumoren) group in Germany has also followed a surgery and surveillance strategy for stage I nongerminomatous MOGCTs.[16]

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Table 3. Event Details

Age (years)	% YST at Diagnosis*	AFP Level (IU/L)		Relapse Confirmed by	Time to Relapse (months)†	Survival	
		Diagnosis	Relapse			Status	Survival Time (months)
Concordant-stage patients‡							
2	2	9,610	153	AFP only	4	Alive	42.1
9	99	3,772	3,773	AFP only	7	Alive	79.6
13	100	497	39	Pelvic mass	5	Alive	35.8
13	60	17,285	915	Retroperitoneal mass	4	Alive	43.3
13	100	26,773	305	Pelvis and retroperitoneum	2	Alive	28.2
13	100	889	446	AFP only	4	Alive	23.4
15	99	44,115	792	Pelvis, liver, pleura	2	Alive	57.7
16	100	56,221	476	Para-aortic mass	1	Alive	29.1
16	50	494	998	Unknown site of mass	1	Dead	16.2
Discordant-stage patients‡							
< 1	Unknown	156	327	Retroperitoneal mass	2	Alive	22.1
10	25	13,310	146	Liver	3	Alive	42.4
11	100	2,220,000	342	AFP only	2	Alive	27.9

Abbreviations: AFP, alpha-fetoprotein; YST, yolk sac tumor.
*Percentage of the tumor that was YST at diagnosis.
†Time to relapse defined as time from initial definitive surgery to first relapse.
‡Concordant or discordant means that central review of stage by study surgeons was either concordant or discordant with stage determined by institution.

The application of a surgery and surveillance strategy beyond the pediatric and adolescent age group is even more limited.[14,16-19] The heterogeneity of histologies included in these adult trials makes it difficult to draw conclusions about the utility of the surveillance approach outside of the pediatric age group.

A difference in surgical philosophy exists between the adult and pediatric approaches to management of ovarian malignancies; adult gynecologic oncologists might argue that the EFS of 52% observed among pediatric patients could be the result of the fact that extensive sampling of lymph nodes, omentum, and peritoneal surfaces, if normal in appearance, was not mandated in the COG surgical guidelines, leading to underdiagnosis of patients with stage > I disease. The adult surgical approach to ovarian cancer is based on experience with epithelial ovarian cancer, in which aggressive local surgical control is critical in management. However, limited information is available regarding the yield and utility of these surgical maneuvers in adult women with malignant germ cell tumors. This issue has been studied in pediatric patients with MOGCTs.[20] Among 131 pediatric and adolescent girls with MOGCTs, pathologic analysis of sampled tissues deemed normal by the surgeon revealed negative findings in all lymph nodes (18 of 18), all random peritoneal biopsies (seven of seven), and most random omental biopsies (22 of 23). In contrast, tissues judged grossly abnormal by the surgeon intraoperatively had malignant tumor in 19 of 46 lymph nodes, 18 of 29 peritoneal biopsies, and seven of 45 omental resections. Of note, five girls were confirmed to have evidence of disease outside the ovary by positive peritoneal cytology alone, confirming the importance of this test. The staging elements found to be of utility in that study constituted the justification for the revised COG surgical guidelines used in this protocol (Table 1). Although it could be argued that a more thorough surgical approach would have detected occult disease and altered the assignment of stage I status in this study, the salvage rate with chemotherapy was equivalent to OS with upfront chemotherapy, and surgical morbidity was minimized. The value of the elements retained in the current COG pediatric surgical guidelines is reinforced by the higher event rate in those patients in whom the guidelines were not followed.

An open surgical approach was expected for assignment of stage I status in this study because an intact delivery of the specimen to pathology was required to confirm capsular integrity. In the pathologic review of the prior intergroup study, we found that visual assessment of capsular integrity by the surgeon was incorrect approximately 20% of the time.[20] Of 51 patients felt to have an intact capsule by the surgeon, nine were found to be penetrated at histology, and two were found to be ruptured. The large size of these tumors in general would have required morcellation of the specimen if a laparoscopic approach had been chosen to deliver the tumor through a small incision. Complete pathologic assessment of the capsule would not have been possible in that situation.

Despite the increased complexity of MOGCTs in pediatric and adolescent female patients, as compared with testicular germ cell tumors, surgery followed by close surveillance resulted in excellent OS. The lower-than-expected EFS in this population forced early closure of the trial before definitive results could be obtained with narrow CIs and precluded analysis of prognostic factors. Among adult men with apparently stage I testicular cancer, certain prognostic factors, such as presence of lymphovascular invasion, portend a much higher risk of relapse. This information is used productively in shared decision making between patients and physicians about whether to proceed with chemotherapy immediately or to undergo surveillance, with the knowledge that 50% of patients with lymphovascular invasion will eventually need chemotherapy. Subsequent studies should be structured with stopping rules based on OS rather than EFS because salvage is so high with chemotherapy, which would allow for a more robust analysis of prognostic factors among women with apparently stage I ovarian germ cell tumors. However, as long as meticulous attention is paid to surgical guidelines, and patients are carefully monitored, approximately 50% to 60% of girls can be spared the potential morbidity of chemotherapy with successful outcome.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Data analysis and interpretation: All authors
Manuscript writing: All authors
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GLOSSARY TERMS

AFP (alpha-fetoprotein): A protein normally produced by the liver of a fetus. The amount of AFP in the blood of a pregnant woman may serve as an indicator for disorders that a growing fetus may have, such as spina bifida, anencephaly, or Down syndrome. Normal values for men and nonpregnant women vary between laboratories and range between 0 and 6.4 IU/mL or 0 and 20 ng/mL (the same as 0 to 20 g/L). In a woman who is 15 to 22 weeks pregnant, the normal values range from 19 to 75 IU/mL or 7 to 124 ng/mL. High values in a pregnant woman may be indicative of an inaccurate gestational age, multiple pregnancies, a fetus with a neural tube or an abdominal wall defect, or a dead fetus. In nonpregnant adults, a high value of AFP may indicate cancer of the liver, testicles, or ovaries.

β-HCG: The beta subunit of the human chorionic gonadotropin.

Event-free survival: Calculated from the date of diagnosis to the date of the first event, which is resistance, relapse, death, or second malignant neoplasm.

FIGO staging: A tumor staging system established and revised by the International Federation of Gynecology and Obstetrics (FIGO) that takes into account the postoperative histopathologic evaluation of the specimen. The FIGO stage classification has prognostic value.

Overall survival: The duration between random assignment and death.

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